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A stereocontrolled total synthesis of (±)-norzizanone

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Abstract

A stereocontrolled total synthesis of (±)-norzizanone **1** has been efficiently accomplished involving base-induced rearrangement of the mesylate **17** as the key step. Aryl participated intramolecular cyclisation of the bromophenol **11** provided the tricyclic dienone **12**, which was stereoselectively converted into the mesylate **17**.

Keywords: terpenes; cyclisation; desulfurisation; hydroxylation; rearrangement.

Norzizanone **1**, a norsesquiterpene ketone, possesses the tricyclo[6.2.1.0^{1,5}]undecane ring system characteristic of the zizaane group of sesquiterpenes, and has attracted considerable attention[1–4] as a challenging synthetic target. The ketone **1** has been efficiently converted into the sesquiterpene zizaene **2** by Coates and Sowerby.[1] The total synthesis of **1** presents an interesting problem in view of the presence of four asymmetric centres and a *trans*-fused hydroindan ring junction. We report herein a highly stereocontrolled synthesis of (±)-norzizanone **1** from the easily accessible (Scheme 1) indane derivative **11**. Intramolecular anionic cyclisation of **11** provided the tricyclic dienone **12** in high yield. Using the functional groups in ring A, the dienone **12** was stereoselectively converted into the *cis*-diol **16**. The corresponding monomesylate **17** rearranged smoothly under appropriate conditions to afford (±)-norzizanone **1** in excellent yield. The present work constitutes a formal total synthesis of (±)-zizaene **2** (Fig. 1).

Treatment of methyl 3-(4-methoxyphenyl)propanoate[5] with MeMgI (4 equiv.) in refluxing Et_2O followed by intramolecular cyclisation of the resulting carbinol with polyphosphoric acid afforded 1,1-dimethyl-6-methoxyindane **3**[6] in 72% overall yield. Oxidation of **3** with CrO_3 furnished the indanone **4** (76%), mp 63–64°C. Alkylation of **4** with ethyl bromoacetate using LDA (1.1 equiv.) as the base provided the keto-ester **5** (73%), which on hydrolysis yielded the keto-acid **6**[7] (92%). Reduction of **6** with $NaBH_4$ in aqueous NaOH followed by catalytic hydrogenation of the crude product furnished the acid **7**, mp 121–122°C in 89% yield. The corresponding methyl ester **8** was reduced with $LiAlH_4$ and the resulting primary alcohol **9**

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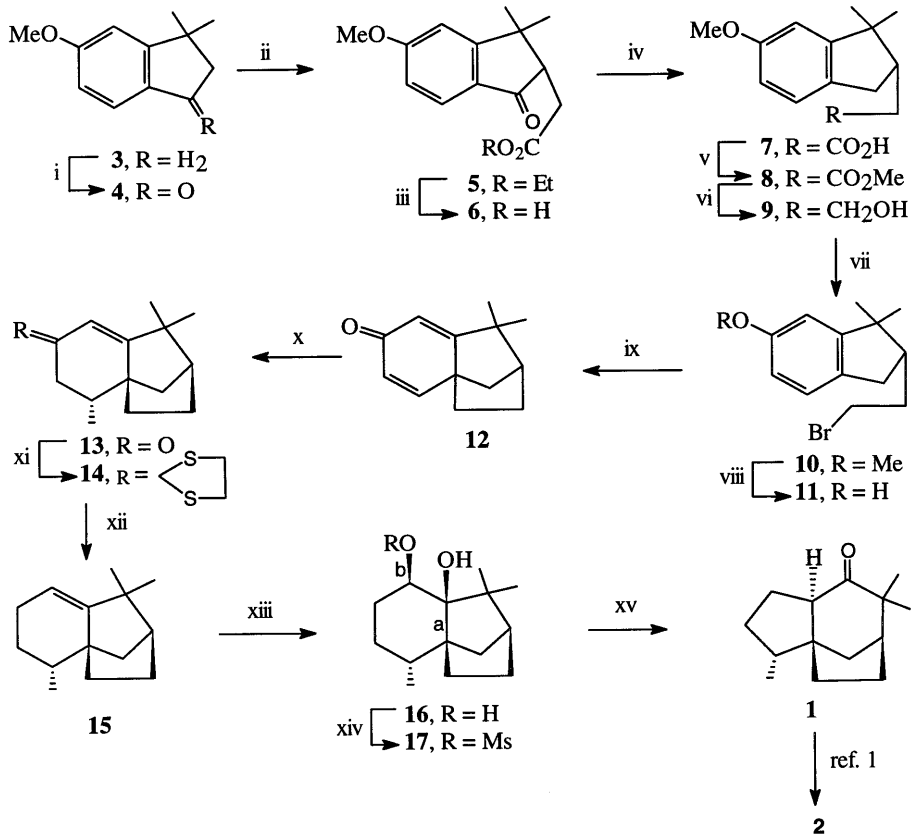


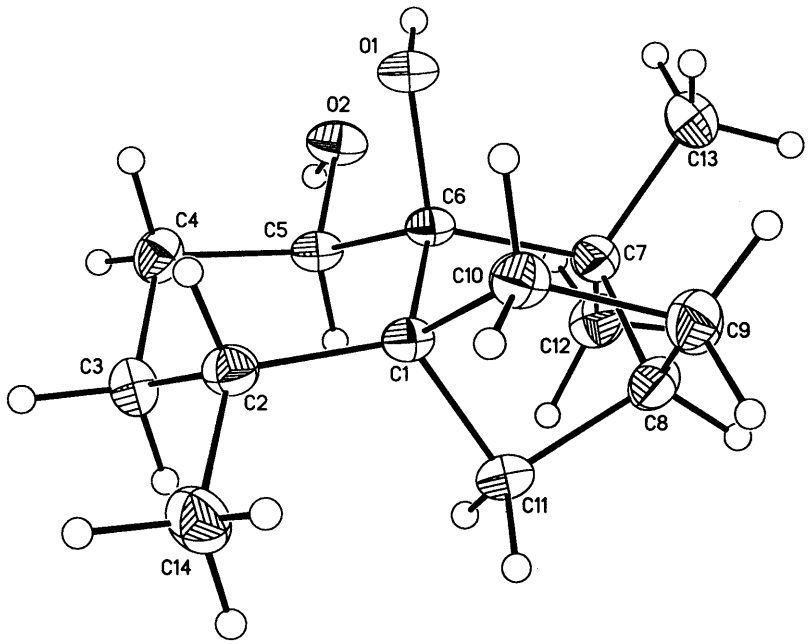
Scheme 1. Reagents and conditions: i, CrO_3, AcOH, H_2O, 5–20°C; ii, LDA, $BrCH_2CO_2Et$, THF, −10 to 20°C; iii, KOH, MeOH, reflux, H_3O^+; iv, $NaBH_4$, aq. NaOH, 25°C, H_3O^+; H_2, 10% Pd–C, AcOH; v, CH_2N_2, Et_2O, 0°C; vi, LAH, Et_2O, reflux; vii, Ph_3P, CBr_4, Et_2O, 25°C; viii, BBr_3, CH_2Cl_2, 0–20°C; ix, *t*-BuOK, *t*-BuOH, 80°C; x, $LiMe_2Cu$, Et_2O, 0°C; xi, $HSCH_2CH_2SH$, MeOH, $BF_3{\cdot}Et_2O$, 25°C; xii, Na, EtOH, liq. NH_3; xiii, OsO_4, C_5H_5N, 25°C; xiv, MsCl, C_5H_5N, 10°C; xv, *t*-BuOK, *t*-BuOH, 20°C

Figure 1.

(95%) was treated with a mixture of Ph_3P and CBr_4 to give the bromoether **10**[7] (80%). Demethylation of **10** with BBr_3 provided the bromophenol **11** (92%). Intramolecular anionic cyclisation[8] of **11** using *t*-BuOK as the base afforded the dienone **12**,[7] mp 72–73°C in 73% yield.

Conjugate addition of $LiMe_2Cu$ to **12** was highly regioselective and stereoselective affording the enone **13**,[7] mp 64–65°C in 85% yield. The stereochemical assignments at C-1, C-2 and C-8 of **13** followed from subsequent transformations leading to the *cis*-diol **16**, the stereostructure of which was established by single-crystal X-ray crystallography. The enone **13** was converted into the corresponding thioacetal **14**[7] in near quantitative yield. Desulfurisation of **14** was effected

efficiently with Na and EtOH in liquid ammonia[9] to give the olefin **15**[7] (87%). Hydroxylation of **15** with OsO_4 furnished the *cis*-diol **16**[7] (85%), mp 116–117°C, which was converted into the monomesylate **17** (90%). As mentioned earlier, the relative stereochemistries at C-1, C-2, C-5, C-6 and C-8 of **16** were determined by X-ray crystallography. The bonds a and b of the diol **16** being antiperiplanar, the monomesylate **17** rearranged[10] smoothly on treatment with *t*-BuOK (1 equiv.) in *t*-BuOH at 20°C to provide the ketone **1**[7] as the sole product in 88% yield. The spectral data of **1** agreed very well with those reported in the literature.



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6. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
7. Selected spectral data for: **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.52 (s, 3H), 2.48–2.58 (m, 1H), 2.92–3.02 (m, 2H), 3.92 (s, 3H), 6.92 (d, 1H, $J=2.4$ Hz), 6.92 (dd, 1H, $J=9$, 2.4 Hz), 7.69 (d, 1H, $J=9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.97, 27.82, 31.29, 41.81, 55.66, 55.66, 107.04, 115.22, 125.68, 126.75, 165.79, 165.93,

177.72, 204.09. **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 3H), 1.31 (s, 3H), 1.85–2.26 (m, 3H), 2.44–2.52 (m, 1H), 2.91–2.98 (m, 1H), 3.38–3.61 (m, 2H), 3.79 (s, 3H), 6.68 (dd, 1H, $J=8.8$, 2.3 Hz), 6.69 (d, 1H, $J=2.3$ Hz), 7.07 (d, 1H, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.53, 26.50, 32.78, 33.28, 34.80, 45.63, 50.08, 55.39, 107.95, 111.72, 124.85, 132.71, 154.35, 158.95. **12**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 3H), 1.19 (s, 3H), 1.25–2.20 (m, 7H), 6.03 (d, 1H, $J=1.5$ Hz), 6.27 (dd, 1H, $J=9.6$, 1.5 Hz), 7.04 (d, 1H, $J=9.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.25, 27.97, 27.97, 33.81, 42.10, 42.33, 48.60, 53.82, 118.06, 130.57, 149.73, 181.42, 187.56. **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (d, 3H, $J=7$ Hz), 1.09 (s, 3H), 1.13 (s, 3H), 1.31–2.69 (m, 10H), 5.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.49, 24.40, 24.55, 26.94, 33.25, 33.52, 39.66, 42.56, 43.80, 46.86, 54.86, 116.83, 182.07, 199.40. **14**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3H), 1.04 (d, 3H, $J=6.5$ Hz), 1.05 (s, 3H), 1.15–2.35 (m, 10H), 3.26–3.44 (m, 4H), 5.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.48, 24.70, 25.23, 28.84, 32.90, 33.88, 38.59, 38.98, 40.42, 41.13, 45.85, 47.22, 52.06, 64.34, 118.48, 155.46. **15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, 3H, $J=7$ Hz), 0.96 (s, 3H), 1.03 (s, 3H), 1.11–1.97 (m, 12H), 5.16 (t, 1H, $J=3.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.20, 21.14, 25.16, 25.70, 26.78, 29.00, 32.35, 35.31, 39.52, 41.45, 47.35, 52.87, 111.05, 154.35. **16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3H, $J=6.4$ Hz), 0.97 (s, 3H), 1.19 (s, 3H), 1.01–2.27 (m, 14H), 3.85 (dd, 1H, $J=10.5$, 5.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.40, 22.97, 24.83, 24.83, 27.34, 31.05, 31.51, 31.55, 32.18, 43.56, 49.73, 57.21, 72.33, 80.00. **1**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, 3H, $J=6.6$ Hz), 1.04 (s, 3H), 1.19 (s, 3H), 1.37–2.13 (m, 12H), 2.93 (t, 1H, $J=8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.19, 20.04, 22.13, 25.71, 26.79, 30.45, 32.15, 36.15, 41.41, 49.03, 49.98, 54.02, 57.50, 216.51.

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